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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,719	ROBL ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner of Record is now Thaian N. Ton of Art Unit 1632.

Applicants' Amendment and Response, filed 9/7/06, has been entered. Claims 1-50 are cancelled; claims 51-53 are pending and under current examination.

No substantive remarks to the Office action, mailed 11/17/05, were filed with the instant amendment, the Examiner responds to Applicants' Remarks filed 5/17/06 in this Office action.

Claim Objections

Claim 51 is objected to because of the following informalities: the term "mitochondrial" is misspelled in line 7 of part (i). Appropriate correction is required.

Double Patenting

The prior rejection of claims 1-17, 32-45 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4-11, 13-19, 24-30, 32-38, 40-52, 58-60 of copending Application No. 09/260,468 is rendered moot in view of the abandonment of this application.

The prior rejection of claims 1-17, 32-45 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-58 of copending Application No. 09/467,076 is rendered moot in view of the abandonment of this application.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214

USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-17, 32-45 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 51, 52, 57, 62, 67, 69, 70 of copending Application No. 10/329,979. Although the conflicting claims are not identical, they are not patentably distinct from each other because each are directed to nuclear transfer methodology encompassing the use of mammalian donor and recipient cells to produce embryonic stem cells. It is noted that dependent claims set forth embodiments that mirror exactly the instant claims.

Applicants' Arguments. Applicants state that they are ready to file a terminal disclaimer, if one is determined to be needed after there is allowable subject matter in this case. See page 6, 2nd ¶ of the Response filed 5/17/06.

Response to Arguments. Because no terminal disclaimer has been filed in the instant case, and the claims are not determined to be allowable, this rejection is maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 51-53 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/922,374. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to methods of cross-species nuclear transfer methods to produce embryonic or stem-

like cells. Both the instant claims and that '374 claims have the same method steps in order to obtain the resultant cells. The instant claims only differ because they are broader, and encompass the subject matter in the '374 application. Particularly, the instant claims recite using a human or mammalian donor cell, and an enucleated animal oocyte for NT methods; the '374 application recites using a differentiated human cell into an ungulate oocyte. Thus, the human donor cell and the ungulate oocyte are encompassed by the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants Arguments. Applicants argue that because the Examiner acknowledged that cross-species nuclear transfer was part of the state of the art at the earliest priority date of the instant application (see Office action mailed 11/17/05, page 12), and their claimed invention discloses an improvement to cross-species nuclear transfer (NT), namely incorporation of mitochondria or mitochondrial DNA derived from a mammalian donor cell into a recipient oocyte of another species, one of skill in the art should have no trouble in practicing this

improvement method to cross-species NT following the disclosure of the specification. Applicants point to various parts of the specification wherein they feel enabling support for this disclosure is to be found. See pages 6-7 of the Response, field 5/17/06.

Response to Arguments. These arguments have been fully considered, but are not persuasive. The Examiner outlines the reasons for the lack of enablement in the rejection below.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention. The claimed invention, as now-amended, is directed to a method of producing embryonic or stem-like cells comprising: i) inserting a desired differentiated human or mammalian donor cell or cell nucleus into an enucleated animal oocyte, wherein such oocyte is derived from a different animal species than the human or mammalian cell, under conditions suitable for the formation of an NT unit, and wherein mitochondria or mitochondrial DNA derived from cell or cells of said donor cell's species is incorporated into said oocyte; ii) activating the resulting NT unit; iii) culturing the activated NT unit until great than the 2 cell developmental stage; and iv) culturing cells obtained from said cultured NT unit to obtain embryonic or stem-like cells. In further embodiments, the mitochondria/mitochondrial DNA is derived from the cells of the donor; and the donor cell is human.

Breadth of the claims. The breadth of the claims encompasses utilizing <u>any</u> human or other mammalian species donor cell with <u>any</u> animal oocyte, to produce embryonic or stem-like cells.

Guidance of the Specification/The Existence of Working Examples. The specification provides general guidance on cross-species nuclear transfer to produce embryonic or embryonic-like stem cells. The working examples in the specification are directed to utilizing human epithelial cells as donor cells, in a NT method using bovine recipient oocytes. The human donor cells were then placed in the perivitelline space of the enucleated, recipient oocyte, and then electrofused. The resultant NT unit was then activated and cultured until day 12 of activation, and NT unit reaching the desired cell number (about 50) were mechanically removed from the zona to produce embryonic cell lines. In particular, the cells from the inner portion of the NT unit were isolated, and grown on fibroblast feeder cells. Table 1 provides guidance with regard to NT units produced, in particular, showing only one NT unit developed to the 16-400 cell stage. See also, Example 1. The specification further teaches that similar results were obtained by the fusion of an adult human keratinocyte line using an enucleated bovine oocyte, wherein one blastocyst was developed. Example 2 provides a protocol to isolate mitochondria from cells to enhance cross-species NT, but no results.

Thus, the specification theorizes that the efficacy of cross-species NT, "[M]ay be enhanced by the introduction of mitochondria or mitochondrial DNA as the same species as donor cell or nucleus. Thereupon, the nucleus DNA of resultant NT units will be species compatible". See page 68, lines, 15-18. However, the specification provides no specific guidance for carrying out the claimed invention, as now-amended, with regard to producing embryonic or stem-like cells for the breadth of species claimed, wherein the mitochondria or mitochondrial DNA from the donor cell is incorporated into the enucleated oocyte from a different species than the donor cell.

State of the Art/Predictability of the Art.

Cross-Species NT Unit Formation. The low level of effectively producing interspecies NT units found in the specification is consistent with results found in

the art. Wolfe *et al.* (cited previously) teach the production of one bison/domestic cow NT unit and 3 goat/cow NT units that developed at least to the morula stage with one of each type forming arresting a blastocyst stage. Furthermore they demonstrated that interspecies NT units were more likely to form if the species were more closely related then distantly related such as with hasmer/cow NT unit, which never developed. Gurdon (cited previously) teaches that more distant species as human and Xenopus have been used to produce NT units. While capable of supporting several cell divisions, the end result was usually arrest at blastocyst stage with irregular blastocysts (p. 300). The state of the art further suggests that more factors such as cytoplasmic and mitochondrial compatibility will be involved in successful interspecies NT (Meirelles *et al.* cited previously; Dominko *et al.*, cited previously). These data presented in the specification as well as instances in the art demonstrate that they techniques are low yielding and unpredictable. An artisan would not know how to use or make the instant invent in a predictable reproducible fashion from the instant specification or the art.

A more recent review by Dominko et al. (1999), cited previously provides a even more general review for the use of distant mammalian species clearly teaching the necessity of testing the compatibilities of cytoplasmic (i.e. mtDNA) and nuclear DNA when practicing interspecies NT (see summary on page 1501). Therefore, based on the art of record only species with closely related nuclear and cytoplasmic genes would be capable of successfully reconstituting the genetic complement necessary for development of an embryo (see summary in abstract). Moreover, the simple reliance of the instant specification on nuclear transfer methodology known in the art fails to address even such limitations of successfully practicing intra-species nuclear transfer (see, for example, Aronson et al., cited previously).

Mitochondrial DNA. The claims as now amended require that mitochondria or mitochondrial DNA derived from the donor cell is incorporated into the oocyte (see step (i) of claim 51). The state of the art is unpredictable with regard to the

role of mitochondrial DNA (mtDNA) and the further development of the NT unit. Various factors, including the species of oocyte used, can complicate successful NT. For example, the post-filing art of Jiang *et al.*(**Frontiers in Bioscience**, 11: 1425-1432, May 1, 2006) review the different fates of donor mtDNA in bovine-rabbit and cloned bovine-rabbit embryos. They teach that a variety of developmental processes are affected by the capacity of mtDNA to produce ATP, including normality of spindle organization, chromosomal segregation, timing of the cell cycle, and morphodynamic processes, including compaction, cavitations, and blastocyst hatching. See p. 1425, 2nd col., 1st ¶. Thus, NT units can have heteroplasmic mtDNA, if the donor mtDNA is included with the donor cell/nucleus. Jiang *et al.* state that, "In the process of NT, mitochondria of donor cells together with the nucleus are transferred into the recipient oocyte. Disharmony between nuclear and mitochondrial genes is thus likely to complicate cloning." See p. 1430, 1st coll, 1st full ¶. They teach that although both bovine mtDNA and rabbit mtDNA could be detected throughout various stages of development prior to implantation, others in the art found that only the recipient mtDNA was found beyond the 16-cell stage, and thus, conclude that rabbit ooplasm has a greater tolerance to foreign mitochondria (p. 1430, 2nd col., 1st ¶). Thus, Jiang *et al.* provide evidence that the art is unpredictable with regard to the species of oocyte that would tolerate foreign mitochondria, and the important role that mitochondria play in embryo development.

Similarly, Chang *et al.*(**Fertility & Sterility**, 80(6): 1380-1387, December 2003) teach interspecies somatic cell nuclear transfer (iSCNT) using human donor cells and bovine enucleated oocytes. They teach the analysis of human mtDNA after NT and found that although bovine mtDNA was detected up to blastocyst stage, the human mtDNA was not detected in either morulae or blastocysts (see Figure 2 and p. 1383, 2nd col., mtDNA Analysis). Furthermore, they teach that many of the blastocysts that were produced had abnormal number of chromosomes

(see Table 3, p. 1385 and p. 1386, 2nd col., last ¶). Because Jiang *et al.* (above) teach that mtDNA have an essential role in embryonic development, in such processes as spindle organization and chromosomal segregation, it is also possible that this abnormality is a reflection of the unpredictability of the NT art in general.

Thus, the art clearly shows that although there has been limited success in producing blastocyst-stage iSCNT embryos, there is a lack of predictability in the art with regard to the maintenance of the mtDNA from the donor cell species. The specification only provides general guidance and a prophetic example of how one of skill could carry out the claimed invention; however, this guidance fails to overcome the unpredictable state of the art.

Embryonic Stem Cells. The specification only teaches that, in using the one NT unit formed, a colony of cells with "ES cell-like morphology" was formed. There is no guidance or any analysis of these ES cells. In particular, the art recognizes that not only morphology of ES cells is important in their identification, but also specific markers and karyotypic analysis must be performed in order to identify ES cells.

For example, Roach & McNeish (**Methods in Molecular Biology**, vol. 185, *Embryonic Stem Cells: Methods and Protocols*, Ed. K. Turksen, Humana Press Inc, Totowa, NJ, 2002, pages 1-15) discuss methods to isolate and maintain mouse ES cells. In particular, they teach that ES cells are isolated from the inner cell mass of the blastocyst stage mouse embryo, and can grow indefinitely in an undifferentiated, diploid state. See page 1, 2nd ¶.

Similarly, Thomson (**PNAS**, 92: 7844-7848, August 1995) discuss the isolation of a primate (Rhesus) embryonic stem cell line, wherein the identification of these ES cells are determined by 1) the potential to differentiate into all derivatives of the three embryonic germ layers, 2) remain undifferentiated in continuous passage; 3) maintain a normal karyotype and 4) express the appropriate cell surface markers, such as alkaline phosphatase, SSEA 3, SSEA4, TRA-1-60 and TRA-1-81. See

Abstract and p. 7844, 2nd col., 1st ¶. Furthermore, Thomson teach the isolation of these ES cells from the inner cell mass of rhesus monkey blastocyst (see p. 7844, col. 2, 2nd ¶, and Materials and Methods, *Cell Line Isolation*). Additionally, Thomson (Science, 282:1145-1147, November 6, 1998) teach the isolation of human ES cell lines from the inner cell mass of human blastocysts and the specific characteristics of these ES cells (p. 1145, 2nd col., 1st ¶).

The Amount of Experimentation Necessary. The specification is not enabling for the breadth of the claimed invention. The specification fails to overcome the above-recited unpredictibilities in cross-species nuclear transfer, the unpredictability in maintenance of the donor mtDNA, the importance of mtDNA in embryonic development, as well as in the production of embryonic or ES-like cell lines for the breadth of species encompassed by the claims. The specification provides no working examples with regard to the method, as instantly claimed, which now encompasses incorporation of the donor mitochondria or mitochondrial DNA into the recipient oocyte. The working example in the specification is only directed to general NT methods, and does not address the production of ES cells when using the claimed method. One of skill in the art would not be able to practice the claimed invention, as broadly claimed, because the specification fails to provide guidance to practice the claimed invention, and the art provides significant teachings of the unpredictability found in the art, with regard to cross-species NT, and producing ES cells from the resultant NT unit.

Because the intended use of the claimed method is to produce embryonic stem cells, one of skill in the art would recognize that the NT unit would need to be able to develop to blastocyst stage, with the expression of appropriate markers and karyotype, in order to produce ES cells. The art clearly shows that there is unpredictability with regard to chromosome abnormalities in cross-species NT, and although the working example in the specification provides guidance with morphology of cells isolated from an inner portion of an NT unit, the specification

provides no guidance with regard to any other art-recognized characteristics of the resultant cells, such that one of skill in the art would recognize that the cells were indeed ES cells. There is no guidance provided by the specification with regard to the appropriate markers expressed by the cells, or showing that the cells have the capacity to differentiate into cells of all three embryonic germ layers, such that one of skill in the art could predictably make embryonic or stem-like cells, as instantly claimed.

Further, claim 51 recites culturing an activated NT unit until "greater than the 2-cell developmental stage" (see part iii). This is not enabled, because the art clearly teaches that, in order to isolate ES cells, they must be isolated from the inner cell mass of a blastocyst. The claims broadly encompass using, for example, a 2-cell NT unit in order to produce ES cells. The art clearly shows that only inner cell mass cells, isolated from a blastocyst (which is greater than 2 cells) would produce ES cells.

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Ex parte Maizel.* Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)).

Accordingly, in view of the unpredictable state of the art with regard to cross-species NT, the fate of mtDNA from the donor cell, the importance of mtDNA in embryonic development, the lack of guidance or teaching with regard to incorporation of the donor mtDNA into the oocyte, the lack of teaching or guidance provided by the specification with regard to the isolation of embryonic or stem-like cells, using the claimed method, as well as the state of the art of producing ES cells, which require isolation of the inner cell mass from a blastocyst, to produce ES cells with particular morphological, karyotypic properties, as well as the expression of specific antigens, and the ability of the cells to differentiate into cells of all three

germ layers, it would have required undue experimentation for one of ordinary skill in the art to practice the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 51-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 51 recites the limitation "said culture NT units" in part (iv). There is insufficient antecedent basis for this limitation in the claim. Step (iii) of the claim relates to culturing a single NT unit, whereas step (iv) requires multiple units, and thus, lacks antecedent basis.

Claim Rejections - 35 USC § 103

The prior rejection of claims 1-17 under 35 U.S.C. 103(a) as being unpatentable over Wolfe *et al.*, Collas *et al.* and Westhusin *et al.* is withdrawn because the combination of the cited art fails to make obvious the claimed invention, with a reasonable expectation of success. In particular, in view of Applicants' amendments to the claims, which now require the incorporation of mtDNA into the oocyte, the art is not found to be predictable, with regard to the generation of an NT unit to produce embryonic or stem-like cells.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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